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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,861	03/05/2001	James R. Broach	60623CIP(50370)	4402

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,861	BROACH ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,53,54,57,59,60 and 120-122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,53,54,57,59,60 and 120-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Please note the change of examiner for this application. *(Please see the Conclusion paragraph for information on any future correspondence.)*

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/8/06 has been entered.

Status of the Claims

Claims 2-52, 55-56, 58, and 61-119 have been canceled as filed on 5/8/06;

Claims 120-122 have been added as filed on 5/8/06;

Claims 1, 53, 54, 57, 59, 60, and 120-122 are presently pending;

Claims 1, 53, 54, 57, 59, 60, and 120-122 are being examined in this application.

Election/Restrictions

Applicant's election of the *"single disclosed species"* of the human bradykinin receptor as the heterologous G protein coupled receptor and the sandwich chimera Galphaq(1-11)-GPA1 (6-467)-Galpaq(355-359) of Example 12, which substitutes both the N and C terminus of GPA1

with 1st and 2nd heterologous subunits derived from the same source, in the reply filed on 8/20/04 was previously acknowledged.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The present application (09/581,861 filed 3/5/2001) claims priority under:

a. 371 of PCT/US98/21168 (filed 10/07/98); and

b. CIP of 08/946,298 (filed 10/7/97) as well as earlier applications.

Upon review of the two above cited documents, the presently claimed (and elected invention) finds disclosure support in the PCT/US98/21168 application (filed 10/07/98) BUT not the 08/946,298 (filed 10/7/97) application which lacks direct or exemplary support for the presently claimed scope of claims e.g. the substitution GPA variants as well as the sandwich chimeras. Accordingly, the present elected claims are granted the filing date of the PCT application (e.g. 10/7/98) for purposes of prior art.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

None of the listed applicants have signed the Oath/Declaration as filed on 6/16/2000.

Drawings

The drawings/figures are objected to because tables and sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. Applicants are advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 C.F.R.§§1.821-1.825 will be published as part of the patent. Applicants should amend the specification to delete any Figures which consist only of nucleic acid or protein sequences which have been submitted in their entirety in computer readable format (i.e. as SEQ ID NO:'s) and should further amend the specification accordingly to reflect the replacement of the Figure by the appropriate SEQ ID NO:.

Appropriate correction is required.

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections Withdrawn

Upon further consideration, the following claim rejection is withdrawn:

Claims 1, 53, 54, 57, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. WO 95/21925 (8/95), Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier), Brown et al. WO 99/14344, and/or Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890 in view of Hamm, J. Biol. Chem. Vol. 273(2) (Jan. 1998) pages 669-672.

New rejections are set forth below.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

Claims 1, 53, 54, 57, 59, 60, 120-122 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating recombinant yeast cells comprising certain heterologous G-protein coupled receptors (GPCR) (e.g. C5a, FPRL, ML1aR etc.; p.91 and 104 of the instant specification) with certain GPA1 chimeric G-protein subunit, does not reasonably provide enablement for any combination of GPCR and mutant G-protein

alpha subunit within any recombinant yeast cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims/ The nature of the invention

The instant claims recite a recombinant yeast cell which comprises:

A.) a heterologous G protein-coupled receptor (GPCR) expressed in the cell membrane of said yeast cell such that signal transduction activity via said receptor is modulated by interaction of an extracellular region of the receptor with an extracellular signal, said heterologous GPCR acting as a surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell; and

B.) a chimeric G protein subunit which comprises an endogenous yeast Gpa1 subunit in which at least the last four C-terminal amino acids of said Gpa1 are replaced with at least the last

four C-terminal amino acids of a first heterologous G protein subunit, and in which the N-terminus of said Gpa1 is operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit, wherein said first and second heterologous G protein subunits are the same or different; such that expression of said chimeric G protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of said yeast cell; and wherein modulation of the signal transduction activity of said heterologous GPCR by an extracellular signal provides a detectable signal.

The breadths of the claims seem to encompass a genus of yeast cells comprising a genus of heterologous G-protein coupled receptors. That is the claims are broadly drawn to any heterologous G-protein coupled receptors, (i.e. any GPCR derived from any sources other than yeast cells). Claims 1 and 53 are also drawn to a genus of chimeric G protein subunit with at least any 4 or 5 C- and N-terminal amino acid substitutions in the yeast Gpa1 subunit. Neither the instant specification nor the claims provide common structure and/or function for the claimed genus of GPCR in combination with the genus of mutant G-protein subunits.

The state of the prior art/ The predictablility or lack thereof in the art

The signal transduction pathway involving G-protein coupled receptor (GPCR) and G-protein are not completely understood in the art. Although the structure of certain GPCR and G-protein heterotrimeric complex have been solved (e.g. Lambright et al., Nature. Vol. 379. 311-319; 1996), the intricate structural interaction between the receptor and the G-protein, as well as the interaction among the various subunits (alpha, beta, and gamma) of the G-protein itself are not clearly defined in the art.

Although the GPCR protein family share common structures such as transmembrane regions and G-protein interaction regions, the specific interaction between different GPCR and G-protein subunits are highly unpredictable. For example, Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004), teach that when using exogenous G-protein coupled receptor as surrogate for pheromone signaling pathway, the yeast cell must be albe to produce a G protein that can be activated by the exogenous receptor (p. 43, para 3 of the reference). The Fowlkes reference also teaches certain Gα subunit does not complement the receptor mediated signal pathway, and "consequently, with some foreign Gα subunits, it is not feasible to simply replace the yeast Gα" (p. 43, lines 30+).

Similarly, Brown et al (WO 99/14344; 3/25/1999; cited in previous an Office action mailed on 10/19/2004), teach "human growth hormone releasing hormone receptor (GHRHR), are incompatible with Gpa1p" (in which Gpa1p is one type of chimeric Gpa1 subunit) (p. 3, liens 10 of the reference). The Brown reference also teaches that a mutant Gpa1 molecule with a five C-terminal amino acid mutation has failed to couple with a GPCR in the pheromone response pathway (p. 27, lines 5+). Furthermore, the Brown reference also teaches "Because of the specificity of a given receptor for one or a small number of the known Gα subunits, different Gα constructs have been required to demosntrate functional coupling activity with the majority of receptors tests" (p. 3, liens 30+). In other words, various experiements must be performed to study the compatibility between the receptor and the G-protein subunit.

Similarly, Busconi et al (Biochem. J. Vol. 328 : 23-31 ; 1997), teach mutations of Gα subunit of the G-protein at the N-terminus (Abstract of the reference). The Busconi reference teaches various numbers mutations (or substitutions) of N-terminus of a Gα subunit, and several

mutations are shown to be imcompatible with the signal transduction pathway (e.g. Table 1 of the reference).

Furthermore, the instant specification also discloses several chimeric Gpa1 mutants (or chimeric) that are not compatible with the tested mammalian GPCRs (p. 92 and 104).

The above discussion illustrates the highly unpredictable nature of combining any GPCRs (derived from various sources) with Gpa1 chimeric (which comprises partial Gα amino acid sequences from various sources). Although there may be suggested methods of overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any GPCRs and Gpa1 chimerics.

The level of one of ordinary skill

The level of skill would be high in order to generate recombinant yeast cells comprising various GPCR and G-protein subunits.

The amount of direction or guidance present/ The presence or absence of working examples

The only guidance and examples present in the instant specification is directed to a certain number of mammalian GPCR and a few numbers of chimeric G-protein subunits with certain mutations, as described, for examples, at pages 92 and 104. There is no guidance described for using GPCR from other organisms and/or any other mutations of the yeast Gpa1 subunit. As discussed above, and as indicated in the instant specification (p. 92 and 104), not all mutations of yeast Gpa1 would be able to couple with a desired receptor, and/or not all GPCR

would be able to couple with a certain chimeric (or mutant) yeast Gpa1 to produce the desired yeast recombinant cells that can have the desired signal transduction ability (pheromone signaling pathway). That is the different GPCR may or may not couple with a certain chimeric Gpa1 subunit (e.g. with 5 C-terminal mutations), and the different chimeric Gpa1 subunit (with various numbers of mutations at either C- and/or N-terminus) may or may not couple with the different heterologous receptors (including mammalian receptors). The working examples provided in the instant disclosure are not structurally or functionally representative of the entire genus of the claimed products.

The quantity of experimentation needed

Due to the unpredictabilities of generating a recombinant yeast cells comprising a heterologous GPCR and a Gpa1 chimeric subunit such as problems with the compatibility of the chimeric G-protein subunit and the heterologous GPCR, and the subsequent problems with downstream signaling pathway, undue experimentation would be required. The art has not demonstrated all the possible GPCR (derived from all sources) in combination with all the different chimeric G-protein subunits. In a more narrowing scope, the art has not demonstrated all the possible GPCR that are compatible with the chimeric Gpa1 subunits. The art has not demonstrated that all the desired GPCR and Gpa1 chimeric can be successfully expressed in yeast cells and would possess the desired signal transduction mechanism. The instant specification and/or claims only provide an invitation to experiment with different combination of GPCR and Gpa1 that may or may not produce the desire recombinant yeast cell. Because the instant specification only provides guidance for only a few examples of yeast recombinant cells

that comprise a certain types of GPCR and Gpa1 chimeric, undue experimentation would be required to produce the claimed genus of recombinant yeast cells.

Conclusion

Due to the non-routine experimentation necessary to determine the compatibilities of various GPCR and Gpa1 chimeric comprised within yeast cells; the lack of direction/guidance presented in the specification regarding the specific requirements for the claimed product; the unpredictability of generating a recombinant yeast cell comprising a heterologous GPCR and a chimeric Gpa1 as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitations "the last four C-terminal amino acids" in lines 8 and 9, and "the first five N-terminal amino acids" in line 11, "the signal transduction activity" in line 15 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Claim 53 recites the limitations "the last four C-terminal amino acids" in lines 8 and 9, and "the first five N-terminal amino acids" in line 11, "the signal transduction activity" in line 16 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Claim 54 recites the limitations "the last five C-terminal amino acids" in line 2, and "the first five N-terminal amino acids" in line 4, "the first 11 N-terminal amino acids" in line 5 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Claim 59 recites the limitations "the last four C-terminal amino acids" in line 2, and "the first five N-terminal amino acids" in line 4 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 59, 121 and 122 are rejected under 35 U.S.C. 102(b) as being anticipated by Pausch et al. WO 95/21925 (8/95 ; cited in previous an Office action mailed on 10/19/2004).

The instant claims recite a recombinant yeast cell which comprises:

A.) a heterologous G protein-coupled receptor (GPCR) expressed in the cell membrane of said yeast cell *such that signal transduction activity via said receptor is modulated by interaction of an extracellular region of the receptor with an extracellular signal, said heterologous GPCR acting as a surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell*; and

B.) a chimeric G protein subunit which comprises an endogenous yeast Gpa1 subunit in which at least the last four C-terminal amino acids of said Gpa1 are replaced with at least the last four C-terminal amino acids of a first heterologous G protein subunit, and in which the N-terminus of said Gpa1 is operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit, wherein said first and second heterologous G protein subunits are the same or different; *such that expression of said chimeric G protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of said yeast cell; and wherein modulation of the signal transduction activity of said heterologous GPCR by an extracellular signal provides a detectable signal.*

The portions in italic of the above cited claim language are construed as intended use of the claimed product of a recombinant yeast cell.

Pausch et al, throughout the reference, teach yeast cells transformed with nucleic acids that encode heterologous G protein coupled receptors (Abstract, Claims 1-29, pp. 3-5, pp. 13-14,

pp. 19-24, and Examples of the reference), which reads on the recombinant yeast cells comprising a heterologous G-protein coupled receptor of **clms 1 and 53**.

The reference also teaches the recombinant yeast cells comprising chimeric "chimeric G-Protein subunits" comprising GPA1 and Gα in which the chimeric is formed by fusing the amino terminal domain of yeast GPA1 and the carboxy terminal domain of a heterologous Gα (pp. 14, lines 17-20, and Claims 17 and 18 of the reference). This reads on the chimeric G protein subunit of **clms 1, 53, and 59**. The reference's teaching also reads on the structural limitation of "at least the last 4" C-terminal amino acids are substituted by " at least the last 4 C-terminal amino acids of a heterologous G protein subunit" of **clms 1, 53, and 59**, because the said chimeric G protein subunit taught by the reference is within the scope of "at least 4 C-terminal amino acids", which encompasses the entire C-terminus.

The reference also teaches inactivating the pheromone response pathway genes, and activating the response pathway through the heterologous G-protein coupled receptor (pp. 3-5, and Examples; especially p. 4 and top of p. 5), which reads on the following intended use recitations of **clms 1 and 53**:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell and wherein modulation of the signal transduction activity of the heterologous GPCR by an extracellular signal provides a detectable signal.

The reference also teaches that the chimeric G protein can be all or a portion of a G protein αβγ complex (p. 3, lines 24+), and the yeast Gα subunit (i.e. Gpa1) is to be associated with heterologous Gβγ subunits (p. 14, lines 4+ and 21+). This reads on the limitation of "the N-terminus of said Gpa1 is operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit" of **clms 1 and 59**, because it is an inherent property of the G protein to comprise all three of the α, β, and γ subunits in the form of a complex to exhibit the proper function of the G-protein, as taught by the reference. The instant specification defines the term "operably linked" as "intended to mean that two polypeptides are connected in manner such that each polypeptide can serve its intended function" at p. 21, lines 28+ of the specification. Thus, any connection or association between two polypeptides that produces the intended function such as G-protein's roles in the signal transduction pathway (GTPase activity, etc.) would constitute as "operably linked" as defined by the instant specification.

This inherent property of the G-protein subunits to associate (or connect) to form a complex is further evidenced by Lambright et al (Nature. Vol. 379. 311-319; 1996). Lambright et al, throughout the reference, teaches the crystal structure of a heterotrimeric G protein comprising α, γ, and β subunits (see Abstract and Figure 1 of the reference). The Lambright reference further teaches that the N-terminus of the α subunit (Gα or Gpa1) interacts with the β subunit domain residues (p. 314, left col. and Figure 2a of the reference) in which the β subunit domain residues are within the scope of "at least the first five N-terminal amino acids" of **clms 1 and 59**.

The reference also teaches using reporter gene to indicate the resulting signal transduction using the recombinant yeast cell comprising the G protein and the G protein receptor (e.g. p. 5, lines 20+), which reads on the indicator gene of **clm 121**.

The reference also teaches various yeast host cells including *Saccharomyces cerevisiae* cells (bridging para of p. 15-16), which reads on the yeast cells of **clm 122**.

Claims 1, 53, 59, and 120-122 are rejected under 35 U.S.C. 102(b) as being anticipated by Fowlkes et al. WO 94/23025(10/94; cited in previous an Office action mailed on 10/19/2004).

Fowlkes et al, throughout the reference, teach "chimeric G-Protein subunits" comprising a chimeric G-protein subunit comprising the yeast G alpha unit (e.g. GPA1) in which at least 10, 20 or 40 (only final 10 or 20 deemed critical: see page 43-top of page 44) of the yeast's C-terminal amino acids are substituted by with a substantially homologous mammalian (or other exogenous) C-terminal amino acids Gα, which reads on the chimeric G-protein of **clms 1 and 53**.

The reference also teaches the yeast cell comprising:

A. a heterologous G-protein coupled receptor (GPCR) which acts as a surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell (e.g. Abstract and p. 12, para 2, p.14, para 4-5 of the reference), which reads on the heterologous G-protein coupled receptor of **clms 1 and 53**; and

B. the above "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit functionally integrates said heterologous GPCR into the pheromone response

pathway of the yeast cell and wherein modulation of the signal transduction activity of the heterologous GPCR by an extracellular signal provides a detectable signal. E.g. see Fowlkes et al. Abstract; pages 7-9; pages 12-17; page 23-25; pages 37-40; pages 43-44, particularly bottom of page 43-top of page 44; examples and claims 1-37 (especially for example claims 1, 28 and 29).

The Fowlkes teaching of yeast comprising alpha chimeras composed of N-terminal yeast alpha subunits fused to at least 10, 20 or 40 C-terminal yeast amino acids (page 43-top of page 44) is within the scope of "at least 4 C-terminal amino acids" as presently claimed in **clms 1 and 53.**

The reference also teaches it is necessary to provide foreign or chimeric Gα or Gβγ subunit in the host yeast cells (e.g. p.14, para 4 and top of p. 44). This reads on the limitation of "the N-terminus of said Gpa1 is operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit" of **clms 1 and 59**, because it is an inherent property of the G protein to comprise all three of the α, β, and γ subunits in the form of a complex to exhibit the proper function of the G-protein, as taught by the reference. The instant specification defines the term "operably linked" as "intended to mean that two polypeptides are connected in manner such that each polypeptide can serve its intended function" at p. 21, lines 28+ of the specification. Thus, any connection or association between two polypeptides that produces the intended function such as G-protein's roles in the signal transduction pathway (GTPase activity, etc.) would constitute as "operably linked" as defined by the instant specification.

This inherent property of the G-protein subunits to associate (or connect) to form a complex is further evidenced by Lambright et al (Nature. Vol. 379. 311-319). Lambright et al,

throughout the reference, teaches the crystal structure of a heterotrimeric G protein comprising α, γ, and β subunits (see Abstract and Figure 1 of the reference). The Lambright reference further teaches that the N-terminus of the α subunit (Gα or Gpa1) interacts with the β subunit domain residues (p. 314, left col. and Figure 2a of the reference) in which the β subunit domain residues are within the scope of "at least the first five N-terminal amino acids" of **clms 1 and 59**.

The reference also teaches the chimeric Gα subunit "in which a portion, e.g., at least about 20 or preferably at least about 40, amino acids, which is substantially homologous with the corresponding residues of the amino terminus of the yeast Gα, is fused to a sequence substantially homologous with the main body of a mammalian Gα" (bridging para of p. 43-44). In other words, the amino-terminal of the chimeric Gα subunit (at least 20 amino acids) is "substantially homologous" with the yeast Gα. The reference also defines the term "substantially homologous" as "at least 50%, more preferably at least 80%, identical in sequence" (p. 23, lines 25+ of the reference). Taking together, for example, an amino-terminal with a 20 amino acid residues would comprise 10 to 16 yeast Gα amino acid residues at the N-terminus of the chimeric Gα subunit. Thus, the reference teaches at least replacing at least the first five amino acids at the N-terminus, as recited in **clms 53**.

The reference also teaches inactivation of endogenous pheromone receptor proteins of yeast cells (p. 55, lines 10+), which reads on the pheromone receptor not produced in functional form of **clm 120**. The reference also teaches that in order to achieve selection or screening, the yeast must have an appropriate phenotype, and host yeast cells having native proteins that are being surrogated would frustrate the genetic selection process (p. 55, lines 10+).

The reference also teaches integrating reporter construct into the host yeast cells (bridging para p. 17-18), which reds on the indicator gene of **clm 121**.

The reference also teaches that the host yeast cell are *Saccharomyces cerevisiae* (e.g. p. 54, lines 15+), which reads on the yeast cell of **clm 122**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 57, 59, 121 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al WO 95/21925 (8/95 ; cited in previous an Office action mailed on 10/19/2004) and

Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004).

Pausch et al, throughout the reference, teach yeast cells transformed with encoding chimeric yeast/heterologous G protein coupled receptors, as discussed supra.

Pausch et al do not specifically teach substituting the lower limit of C-terminal amino acids (e.g. four amino acids) of GPA1 or substitution of the last five (5) C-terminal GPA1 amino acids, as recited in **clm 57.**

However, the Pausch reference teaches that (p. 14 of the Pausch reference):

a. the "carboxyl terminal domain" of GPA1 can be substituted by the carboxyl terminal domain of a heterologous Galpha; and

b. that "One can easily determine which configuration is best suited for adequate coupling to a particular heterologous receptor by simply constructing vectors as taught herein and measuring the signaling of ligand binding in response to a given assay"

Accordingly, it would be obvious to one of ordinary skill in the art at the time of applicant's invention to determine optimum minimum C-terminal GPA1 length necessary to obtain coupling as well as additional amino acids encompassing such a minimum number (e.g. 5, 6 ... entire C-terminus) for a particular heterologous receptor.

Alternatively, in this regard, the **Conklin** reference provides evidence that substitution of "at least four C-terminal" Galpha amino acids are necessary (e.g. both –3 and –4 positions) in order to permit coupling to a new receptor (e.g. heterologous receptor). See e.g. Abstract and data obtained therein.

Thus, in light of the Conklin reference teaching, the selection of "at least four C-terminal GPA1 amino acids" or 5 or more up to the entire C-terminus, for substitution with the corresponding C-terminal heterologous Galpha would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to obtrain coupling to a particular heterologous receptor.

A person of ordinary skill in the art would have been motivated at the time of the invention to substitute the desired number of C-terminal residues such as five residues, because Pausch teaches the need to optimize chimeric G-protein subunit by mutating (or substituting) certain numbers of amino acid residues at the C-terminus, and Conklin reference teaches specific number of mutations (such as five residues) at the C-terminus would allow binding to a heterologous receptor as discussed above.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications because the techniques for generating such recombinant yeast cells comprising the desired heterologous receptor and chimeric G-protein subunits are known in the art as taught by Pausch et al and Conklin et al.

Claims 1, 53, 57, 59, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al WO 95/21925 (8/95 ; cited in previous an Office action mailed on 10/19/2004) and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004) as applied to claims 1, 57, 59, 121 and 122

above, and further in view of Fowlkes et al. WO 94/23025(10/94; cited in previous an Office action mailed on 10/19/2004).

Pausch et al, throughout the reference, teach yeast cells transformed with encoding chimeric yeast/heterologous G protein coupled receptors, as discussed supra.

Conklin et al, throughout the reference, teach mutations of the carboxyl-terminal mutations of G-protein α subunit, as discussed supra.

Both Pausch et al and Conklin et al, do not specifically teach replacement of amino acid residue at the N-terminus of the chimeric G protein subunit, as recited in **clm** 53, and an endogenous yeast pheromone receptor protein is not produced in functional form, as recited in **clm 120**.

However, **Fowlkes et al**, throughout the reference, teach recombinant yeast cells comprising a heterologous G-protein coupled receptor, and a chimeric G-protein subunit as discussed supra. The reference also teaches inactivation of endogenous pheromone receptor proteins of yeast cells (p. 55, lines 10+), which reads on the pheromone receptor not produced in functional form of **clm 120**. The reference also teaches that in order to achieve selection or screening, the yeast must have an appropriate phenotype, and host yeast cells having native proteins that are being surrogated would frustrate the genetic selection process (p. 55, lines 10+).

Fowlkes et al also teach replacement of amino acid residues (such as 5 amino acid residues substitution at the N-terminus), as discussed above under the 102 rejection over Fowlkes et al. The Fowlkes reference also teaches the need of designing an exogenous (or heterologous G protein) that can be activated by the heterologous G-protein coupled receptor, and thus enabling the proper signal transduction pathway activation (p. 43, lines 16+ of the reference).

A person of ordinary skill in the art would have been motivated at the time of the invention to inactivate an endogenous G-protein receptor (a pheromone receptor), because the in activation is necessary to carry out the intended screening or step when using a heterologous receptor as a surrogate for the endogenous receptor, as taught by Fowlkes et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to design an appropriate chimeric G-protein subunit comprising the necessary mutations such as 5 amino acid substitution at the N-terminus, because Fowlkes et al teach the need to design heterologous G-protein subunit that is compatible with the expressed heterologous G-protein coupled receptor.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications because the techniques for generating such recombinant yeast cells comprising inactivated endogenous receptor and heterologous G-protein subunits are known in the art as taught by Fowlkes et al.

Claims 1, 53, 57, 59, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004) and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004).

Fowlkes et al, throughout the reference, teach recombinant yeast cells comprising a heterologous G-protein coupled receptor, and a chimeric G-protein subunit as discussed supra.

Fowlkes et al do not teach substituting the lower limit of C-terminal substitution (e.g. four amino acids) of GPA1 or substitution of the last five (5) C-terminal GPA1 amino acids, as recited in **clm 57**.

However, in this regard, the Conklin reference provides evidence that substitution of "at least four C-terminal" Galpha amino acids are necessary (e.g. both –3 and –4 positions) in order to permit coupling to a new (e.g. heterologous receptor). See e.g. abstract and data obtained therein.

Thus, in light of the Conklin reference teaching, the selection of "at least four C-terminal GPA1 amino acids" or 5 or more up to the entire C-terminus, for substitution with the corresponding C-terminal heterologous Galpha would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to obtain coupling to a particular heterologous receptor.

A person of ordinary skill in the art would have been motivated at the time of the invention to substitute the desired number of C-terminal residues such as five residues, because Conklin reference teaches specific number of mutations (such as five residues) at the C-terminus would allow optimization of the mutated G-protein subunit and binding to a heterologous receptor as discussed above.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications because the techniques for generating such recombinant yeast cells comprising the desired heterologous receptor and chimeric G-protein subunits are known in the art as taught by Fowlkes et al and Conklin et al.

Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al (WO 95/21925; 8/95; cited in previous an Office action mailed on 10/19/2004), Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004), and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004) as applied to claims 1, 53, 57, 59, and 120-122 above, and further in view of Hamm, (J. Biol. Chem., Vol. 273(2) (Jan. 1998) pages 669-672; cited in previous an Office action mailed on 10/19/2004).

The teaching of the **Pausch et al, Fowlkes et al, and Conklin et al**, as discussed in the above rejections, is hereby incorporated by reference in their entirety. As discussed above, the above references teach recombinant yeast cells comprising

A.) a heterologous G-protein coupled receptor (GPCR) which act as a surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell; and

B.) a chimeric G-Protein subunit such that expression of the chimeric G-protein subunit comprising a GPA1 subunit C-terminally substituted with at least the last four C-terminal amino acids, and at least five amino acid substitution at the N-terminus of heterologous G alpha protein subunits such that functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell, wherein modulation of the signal transduction activity of said heterologous GPCR by an extracellular signal provides a detectable signal.

Pausch et al, Fowlkes et al, and Conklin et al do not teach additionally modify the N-terminus portion of GPA1 to comprise at least the first five N-terminal amino acids replaced with 1st 11 N-terminal amino acids of a 2nd heterologous G protein subunit, as recited in **clms 54 and 60.**

However, **Hamm** teaches the structure and role of the G protein heterotrimer; particularly the different Galpha subunits and their corresponding receptors (e.g. including bradykinin: see page 669; page 670, right column). The Hamm reference teaches that in addition to the C-terminus of G protein alpha subunits being critical in determining receptor-G protein specificity (as discussed in the above Pausch, Fowlkes, and Conklin references), the N-terminus of the alpha G-protein subunit also appears to be involved in promoting heterologous receptor contact or coupling. E.g. see Abstract; page 669, especially right column; the figures, especially figures 1 and 2, but particularly figure 2 and the role of the 1st N-terminal 23 amino acids of Galpha and rhodopsin receptor)

Accordingly, the Hamm reference would provide motivation to one of ordinary skill in the art at the time of applicant's invention to further modify the chimeric Galpha protein subunits obtained by the Pausch, Fowlkes, and Conklin references by linking or substituting into the N terminal portion of the reference chimeras corresponding heterologous amino acids in order to obtain sandwich chimeras (e.g. N-term heterologous-GPA1-C terminal heterologous) that can be screened for different degrees (e.g. increased/decreased) of heterologous receptor coupling.

The determination of the optimum number of N-terminally linked or substituted heterologous amino acids (e.g. at least 5; i.e. 11) with regard to a particular heterologous receptor and corresponding chimera construct was well within the skill of the art utilizing art-recognized screening techniques. E.g. see Pausch, Fowlkes, and Conklin references and assays disclosed therein.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to additionally modify the N-terminus portion of GPA1 of the Pausch,

Fowlkes, and Conklin references chimeras to replace "at least the first five N-terminal amino acids with the 1st 11 N-terminal amino acids of a heterologous G protein subunit and arrive at the presently claimed sandwich chimeras with a reasonable expectation of success of obtaining modified chimeras which possessed varying degrees (e.g. increased/decreased) of heterologous receptor coupling for use in screening assays (e.g. receptor agonists/antagonists).

Discussion and Answer to Argument

Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants have pointed out that the claim rejections under 35 U.S.C. § 102 are withdrawn as set forth in the office Action mailed on July 8, 2006.

The examiner concurs with the applicant that the claim rejections under 35 U.S.C. § 102 are withdrawn, however, new claim rejections under 35 U.S.C. § 102 are set forth above in the instant Office action.

Applicants argue that the previous Office action did not met the three criteria for establishing a prima facie case of obviousness:

1.) teach or suggest all element;

2.) suggestion or motivation to combine the reference teachings; and

3.) reasonable expectation of success.

In responds to applicant's argument that the references do not teach all elements, applicants are respectively referred to the above art rejections under 35 USC 102 and 103, and

the reason of records. Applicants' traversal over the previous obviousness rejection is based on the analysis of the individual reference, but is not based on all the cited reference as a whole. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicants' argument that there is no motivation to combine all the references (Pausch, Conklin, Fowlkes, and Hamm), applicants' are directed to the above obviousness rejections in which the motivations for combining the references are discussed in detail, especially for mutations of the G-protein subunits in both of the N- and C-terminus.

Specifically, applicant's argue that the Hamm reference does not provide motivation to modifiy the N-terminus of Gpa1. As discussed in the rejection above, the Hamm reference specifically teaches that the N-terminal regions of the alpha subunit along with the C-terminal region of the gamma subunit are both sites of lipid modification suggesting *a site of membrane attachment* (e.g. emphasis provided: see Hamm p. 669, right column 2nd full paragraph). Additionally evidence provided by references cited by Hamm leads to the conclusion by the Hamm reference that "A larger region of the C-terminal region of the Galpha subunits, as well as the N-terminal helix, has been *implicated in receptor contact* "(emphasis provided: See Hamm p. 669, right column, penultimate paragraph). Accordingly, in contradistinction to applicant's argument, the Hamm reference does specifically teach and/or suggest that the N-terminus of G protein alpha subunits is critical to promoting heterologous receptor contact or coupling.

Applicant further argues that "there is no teaching in the Hamm reference (or any of the other references), as to which amino acids in the N-terminus should be linked or substituted.

The Examiner respectfully disagrees.

Initially, it is noted that the claimed invention broadly encompasses the linking to or replacing *at least the first five amino acids* of the N-terminus of GPA1; but would encompass the entire N-terminus.

Additionally, as pointed out in the rejection above, the Hamm reference teaches and/or suggests that the N-terminus of the alpha G-protein alpha subunit is involved in promoting heterologous receptor contact or coupling. E.g. see Abstract; page 669, especially right column; the figures, especially figures 1 and 2. More particularly the reference points to the role of the 1st N-terminal 23 amino acids of the G-protein alpha subunit. See e.g. Figure 1, but particularly figure 2 and the role of the 1st N-terminal 23 amino acids of Galpha and rhodopsin receptor.

Accordingly, applicant's claims broadly encompass operably linking and/or substituting 5 or more (e.g. the entire N-terminus) amino acids of the N-terminus. In this respect, the reference provides guidance as to linking and/or substituting of 1 or more N-terminal amino acids up to the 23rd amino acid.

Applicant further argues that the examiner is applying the references (Hamm reference) as in an "obvious to try" rationale. This argument was considered but deemed nonpersuasive for the following reasons.

The Examiner is not applying an improper "obvious to try" rationale in support of an obviousness rejection. Regarding 'obvious to try':

> "The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been

> obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." See In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted)

In contradistinction to applicant' s argument, the Hamm reference provides a clear suggestion and guidance as to how and where to modify the prior art chimeric proteins to produce the claimed invention along with evidence suggesting the modification would be successful; and further enabling methodology (recombination;mutagenesis etc.) to achieve such modification is known in the art and further discussed in the primary references. Accordingly, the above obviousness rejection does not employ an improper 'obvious to try' rationale.

Additionally, it is noted that reasonable expectation of success and not absolute certainty is the standard for obviousness.

In the present instance although the Hamm reference admits that the C-terminus of the alpha subunit is the best characterized receptor contact region, the reference nevertheless provides evidence (as discussed above) that implicates the N-terminus in receptor contact and membrane attachment. Accordingly, the Hamm reference provides motivation to one of ordinary skill in the art to modify the N-terminus of alpha G-protein subunit in a manner analogous to that performed on the C-terminus in accordance with the the Pausch et al, Fowlkes et al, and Conklin references with a reasonable expectation of making a yeast cell comprising a chimeric G-protein subunit and heterologous G-protein-coupled receptor which act as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell .

In response to applicants' argument that the previous Office action has not shown a reasonable expectation of success, applicants are respectively directed to the above obviousness rejection in which the reasonable expectation of success is discussed for each of the obviousness rejection.

Applicants also argue that the examiner relies on no less than five references in making the obviousness rejection, and such reliance belies the alleged obviousness of the claimed invention.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1, 53, 59 and 120-122 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,864,060 in view of Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004).

The '060 patent claims a yeast cell comprising: 1.) a heterologous G protein coupled repetor; and 2.) a non-naturally occurring G protein subunit (Claim 1 of the reference patent). The '060 patent further claims the non-naturally occurring G protein subunit is a chimera between yeast and mammalian G protein subunit (claim 2 of the reference). The reference patent also claims an indicator gene in the yeast cell (claim 4 of the reference).

The '060 patent does not specifically claim the N- and C-terminal substitutions of the chimeric G-protein subunit, and also does not claim the N-terminal of the chimera is "operable linked" to another G-protein subunit.

However, Fowlkes et al, throughout the reference, teach yeast cells transformed with nucleic acids that encode heterologous G protein coupled receptors and chimeric G-protein subunit with the subunit comprising a yeast Gpa1 subunit, as discussed supra. The reference also teaches the specific N- and C-terminal amino acid replacements, and the N-terminal is "operably linked" to another G-protein subunit, as discussed supra.

Fowlkes et al also teaches the need of designing an exogenous (or heterologous G protein) that can be activated by the heterologous G-protein coupled receptor, and thus enabling the proper signal transduction pathway activation (p. 43, lines 16+ of the reference).

A person of ordinary skill in the art would have been motivated at the time of the invention to design an appropriate chimeric G-protein subunit comprising the necessary mutations such as 5 amino acid substitution at the N-terminus, because Fowlkes et al teach the need to design heterologous G-protein subunit that is compatible with the expressed heterologous G-protein coupled receptor.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications because the techniques for generating such recombinant yeast cells comprising inactivated endogenous receptor and heterologous G-protein subunits are known in the art as taught by Fowlkes et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1639
8/21/2006

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PATENT EXAMINER